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UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE INCORPORATED,

Plaintiff,

v.

VYSIS, INC.,

Defendant.

No. 99cv2668 H (AJB)
JUDGE MARILYN L. HUFF

MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT OF PLAINTIFF GEN-PROBE INCORPORATED'S MOTION FOR PARTIAL SUMMARY JUDGMENT

DATE: May 29, 2001
TIME: 10:30 a.m.
DEPT: Courtroom 1

TABLE OF CONTENTS

TABLE OF AUTHORITIES

PAGE(S)

CASES

TABLE OF AUTHORITIES
(CONTINUED)

PAGE(S)

STATUTES

I. INTRODUCTION

Plaintiff Gen-Probe moves for partial summary judgment under Counts One and Three of its Second Amended Complaint that its nucleic acid test for human immunodeficiency virus ("HIV") and hepatitis C virus ("HCV") does not literally infringe the claims of U.S. Patent No. 5,750,338 ("the '338 Patent")[1]. Gen-Probe's HIV/HCV test is used to screen donated blood using a novel and highly sensitive technology that "amplifies" even a small amount of virus in a sample to a level where it can be detected, using Gen-Probe's own patented method of "Transcription-Mediated Amplification" or "TMA."

Gen-Probe's TMA amplification process uses "primers" that attach to carefully selected portions (or "sequences") of the target organism's nucleic acids. These sequence-specific primers are carefully researched and designed to attach to unique nucleic acids of the target organism, so that the test produces accurate results. The single issue presented by this motion is whether the claims of the '338 patent encompass nucleic acid amplification methods such as TMA, which use sequence-specific primers. By this motion, Gen-Probe shows that the claims of the '338 patent in fact encompass only amplification methods using *non-specific* primers and enzymes. Therefore the claims of the patent do not encompass Gen-Probe's TMA products, and summary judgment should be granted.

As discussed below, the scope of the patent claims is determined primarily from the face of the patent. In this case, the result required by such analysis is confirmed by unequivocal additional evidence. For example, on December 15, 1989, the Director of Business Development and Licensing for Gene-Trak Systems (the predecessor to defendant Vysis, Inc.) clearly described the invention of the '338 patent:

> Cetus, Sibia, Salk, Biotechncia, etc. [e.g., other amplification methods] all claim **specific** primers for amplification, whereas the present invention claims use of the opposite, namely, **non-specific** primers or promoters.

(Exhibit 1 at page 2, emphasis in original).

[1] The '338 Patent is attached as Exhibit 8 to Gen-Probe's accompanying Notice of Lodgment of Exhibits. Unless otherwise specified, all references to exhibits refer to exhibits lodged with such Notice.

Section I of this memorandum sets forth scientific background intended to assist the Court in its analysis of the case. In Section II of the memorandum, Gen-Probe shows that the '338 patent must be construed to cover only non-specific amplification, based on:

1. An analysis of the patent itself, which clearly describes only non-specific amplification methods and states that sequence-specific primers are not necessary when the methods of the patent are used;

2. The expert declaration of Joseph O. Falkinham, III, Ph.D.;

3. Documents and testimony that clearly establish the inventors' and the patents owner's admissions as to scope of the patent claims.

Finally, in section III of the memorandum, Gen-Probe shows that its HIV/HCV test does not literally infringe[2] the claims of the '338 patent, properly construed.

II. SCIENTIFIC BACKGROUND

The '338 patent relates generally to methods for use in nucleic acid diagnostics, including the use of nucleic acid "probes" to detect infectious organisms. In particular, the patent relates to methods by which nucleic acids may be "captured" onto solid supports and copied (or "amplified"), so that small quantities of these nucleic acids may be then detected by probes.

In order to construe the claims of the '338 patent, a very basic familiarity with nucleic acid amplification is required. In particular, it is necessary to understand the distinction between "specific" and "non-specific" primers and enzymes, used in the amplification process to mark the nucleic acid sequences to be copied. A brief overview of the relevant technology is set forth in this section.

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[2] Several inconsequential distinctions arise in this case from the fact that Gen-Probe has licensed the '338 patent. First, because this is a declaratory judgment action brought by Gen-Probe, the plaintiff-defendant positions are reversed from a typical infringement suit. Thus, the patent owner, Vysis, is the defendant. Second, despite the fact that plaintiff Gen-Probe holds a license to the '338 patent and cannot technically be found to "infringe" the '338 patent, the legal issue of infringement is central to Counts One and Three of Gen-Probe's Second Amended Complaint. For example, the terms of the license impose obligations only upon those products of Gen-Probe that would constitute an infringement of the '338 patent but for the license. For the sake of convenience and familiarity, this motion uses the same terminology applicable to a suit for patent infringement.

A. Nucleic Acids

Nucleic acids are molecules that store and transfer genetic information in all living organisms. The two main types of nucleic acids are DNA (deoxyribonucleic acid) and RNA (ribonucleic acid). DNA functions as a stable repository of genetic information, while RNA typically serves to transfer the information stored within DNA to the cell's machinery for making proteins.

DNA and RNA are both composed of chains of chemical sub-units called "nucleotides." Each nucleotide has three components: a sugar ("deoxyribose"), a phosphate group, and a "base" containing nitrogen. There are four types of nucleotides in DNA, each of which has a different base: adenine, thymine, guanine, or cytosine (abbreviated A, T, G, and C). These four "bases" form the building blocks of all DNA[3]. The sugar and phosphate groups within each nucleotide form the backbone of the DNA molecule, linking together the individual nucleotides that make up the molecule. (See Illustration, Exhibit 2).

The "sequence" of the individual A, T, G, and C nucleotides in a DNA molecule encodes the genetic information that instructs the cell how to make particular proteins. Because DNA sequences determine which proteins a cell will make, it is differences in their DNA sequences that make the cells of one organism differ from the cells of another.

DNA in cells ordinarily occurs in a molecular structure in which two "strands" of DNA are specifically bound to one another. Double-stranded DNA is often depicted as a ladder in which each strand forms one side of the ladder and one half of a rung of the ladder. Each nucleotide's base is chemically bonded to a nucleotide base on the opposite strand to form the rungs of the ladder. In its normal state, the ladder is twisted spirally, forming a three-dimensional "double helix" structure. (See Illustration, Exhibit 3).

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[3] RNA also consists of a sequence of four bases comprised of four different nucleotides. The four nucleotides contained in RNA are identical to DNA except that thymine (T) is replaced by uracil (U). Unlike DNA, RNA typically exists as a single strand. However, the nucleotides of RNA have a similar attraction to complementary nucleotides (A binding to U, and C binding to G) and two RNA molecules, or an RNA and a DNA molecule, can form a double helix in which the two strands are joined by complementary base pairing.

In double-stranded DNA, the nucleotides on opposite sides of the ladder are always paired in a precise way. An "A" nucleotide binds only to a "T" nucleotide on the opposite strand, and vice versa. Likewise, a "G" nucleotide binds only to a "C" nucleotide, and vice versa. (See Illustration, Exhibit 4.)

Each combination of an "A" nucleotide with a "T" nucleotide (or a "C" with a "G") is referred to as a "base pair." The way in which each type of nucleotide binds only to one other type of nucleotide is called "complementary base pairing." As a result of complementary base pairing, the sequence of nucleotides on one strand of a DNA molecule necessarily determines the sequence of nucleotides on the opposite strand.

B. Nucleic Acid Probes

The "attraction" of a nucleotide sequence to its "complementary" sequence allows a scientist to use pieces of nucleic acid as "probes" to detect the presence of a target nucleic acid in a test sample. If two complementary pieces of DNA (or RNA) are present in a solution under the right conditions, the complementary bases will come together and bind to form double strands. This method is commonly known as "nucleic acid hybridization." Nucleic acid hybridization techniques can be applied in a diagnostic test to detect an infectious organism (the "target" organism) by the use of a probe that is designed to bind specifically to a nucleic acid sequence that is known to be unique to the target organism. The sample suspected of containing the infectious organism is treated to break open the organism, release its nucleic acids into the solution, and render them single-stranded, if necessary. The specific probe is then added, and conditions conducive to hybridization are established. (See Illustration, Exhibit 5.)

In theory, if the target organism is present in the sample, the "probe" should bind to the target organism's nucleic acids because the sequence of the probe has been designed to be complementary to them. By attaching a detectable "label" to a probe, scientists are able to determine how much, if any, probe has bound to sequences from the target organism.

Nucleic acid probes are generally designed based on the fact that each species of organism has its own unique genome. By the early 1980's, scientists were routinely determining the specific nucleotide sequences of different species' DNA and RNA and searching for sequences that were

common to and different among various organisms. Using this information, scientists could design probes that, under the right conditions, would bind to nucleic acid sequences characteristic of a specific target organism and not to sequences of other organisms.

However, related species have substantial portions of their DNA that are identical. Generally, more closely related species have more DNA sequences in common. DNA sequences that are common to a target organism and other organisms can interfere with the specific detection of the desired target. For example, the sequence CGTAG shown in the Illustration of Exhibit 2 might appear in the DNA of many species. A probe that is complementary to this sequence would bind to the DNA of the target organism, and also to the DNA of other species that contain the same sequence. Samples that did not contain the target organism, but did contain one or more of the other species, would be falsely analyzed if such a probe were to be used in a diagnostic test.

Thus, it is desirable to have a probe that binds only to DNA of the target pathogen and not to DNA contained in other organisms. A probe that consists of a DNA sequence unique to the target organism and which therefore binds exclusively to the DNA of the target organism, and not to DNA of other organisms, is said to be "specific" for the target organism.

C. Target Capture

Target capture techniques are used in nucleic acid methods to isolate a particular nucleic acid of interest prior to detection or other steps. In target capture methods, the target nucleic acid is bound to a solid support, such as a filter, particle, or a bead, which allows the target to be removed from the sample in which it was originally contained. The immobilized target nucleic acid is directly detected with a probe, amplified prior to detection, or used for other purposes.

The target nucleic acid can be immobilized on the solid support either by direct attachment or by the use of an intermediate "capture probe." A capture probe is a nucleic acid sequence that is designed to bind with the target organism's DNA or RNA and also attach to the solid support (See Illustration, Exhibit 6).

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D. Amplification

Often, it is necessary to detect very small numbers of infectious organisms in a sample. This is particularly true when screening for the presence of the organism in the absence of a full-blown infection. Examples include screening blood intended for transfusion for the presence of viruses such as HIV. In these situations, the presence of even small numbers of organisms may lead to the transmission of infection from one individual to another.

Scientists have long understood that detection of a small number of organisms in a sample requires that the number of "target" organisms be increased in number in order to achieve a detectable level. There are many ways to accomplish this. For example, one classic way to detect low numbers of organisms is to transfer the sample to culture media that will support the growth of the organism. After a suitable time, the number of organisms will generally have increased sufficiently to allow them to be detected directly by hybridization or other methods.

A faster approach is to increase the target organism's nucleic acid through processes known as "nucleic acid amplification." Amplification procedures are generally performed with enzymes and primers. Enzymes are protein molecules that catalyze biological reactions. "Polymerase" enzymes are used to copy a DNA or RNA strand to make its complement. Such naturally occurring enzymes are normally used in cellular processes to make copies of the organism's genes to be passed on to its progeny.

Scientists have learned to use enzymes such as polymerase to increase the amount of a DNA or RNA in a sample up to a billion-fold. By making copies of the target organism's nucleic acids, the amount of target that is available to bind with a probe in a detection step is increased to easily detected levels. One of the most famous amplification techniques is the "polymerase chain reaction" (PCR), which uses DNA polymerase and specific primers to multiply specific nucleotide sequences within a nucleic acid. Dr. Kary Mullis received the Nobel Prize in chemistry for his 1983 invention of PCR.

"Primers" are short pieces of DNA that are used in amplification methods to cause an enzyme such as DNA polymerase to start its copying action at a certain point along a nucleic acid sequence. Like probes in the detection step, primers work by binding (hybridizing) to a

complementary nucleotide sequence in the target nucleic acid. DNA polymerase then copies the target nucleic acid beginning at the point where the primer attached. (See Illustration, Exhibit 7.) The procedure can be repeated many times, resulting in copies of the copies. This process of "geometric" or "exponential" amplification produces millions of copies of the target segment that is bounded by the sites where the primers attached.

Primers used in amplification processes can be either specific or non-specific. "Specific" primers are carefully designed to bind only to a pre-selected nucleic acid sequence of a particular target organism, usually a sequence selected to be unique to that organism. Non-specific or "random" primers can be used with DNA polymerases to copy random portions of the nucleic acid sequence of the target organism. When random primers are used, the resulting amplification process is referred to as "non-specific" because DNA synthesis begins at random locations all over the target nucleic acid and any other nucleic acids that may be present in the sample are also amplified. Using random, non-specific primers avoids the work required to select, make, and test specific primers for each individual target organism.

Another form of enzymatic amplification makes copies of RNA from a DNA sequence using an enzyme called "transcriptase." Transcriptases are types of polymerase that make an RNA sequence that is complementary to an initial DNA sequence. The process of making this RNA copy ("transcription") may also be specific or non-specific. Transcriptases do not use primers but instead begin RNA synthesis at special DNA sequences ("promoter sequences"). Many transcriptases only carry out specific transcription in the presence of other special protein factors (often called "subunits"). In the absence of these subunits, the "core" transcriptase enzyme binds randomly to the DNA and starts making RNA molecules at multiple random sites.

III. THE CLAIMS OF THE '338 PATENT MUST BE LIMITED TO NON-SPECIFIC AMPLIFICATION METHODS

By this motion, Gen-Probe moves for summary judgment on the issue of literal infringement inherent in Counts One and Three of the Second Amended Complaint. A determination of the issue of infringement involves a two-step analysis. First, the Court must construe the claims at issue in order to determine their meaning and scope. Second, the Court

must determine whether the claims, as properly construed, encompass the technology used by Gen-Probe. *WMS Gaming Inc. v. International Game Technology*, 184 F.3d 1339, 1346 (Fed. Cir. 1999); *Zelinski v. Brunswick Corp.*, 185 F.3d 1311, 1315 (Fed. Cir. 1999). The first step of the Court's analysis, construction of the claims, often decides the question of infringement. *Netword LLC v. Centraal Corp.*, 242 F.3d 1347, 1350 (Fed. Cir. 2001).

Claim construction, the judicial statement of what is and is not covered by the technical terms and other words of the claims, is a question of law to be decided by the Court alone. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979 (Fed. Cir. 1995), *aff'd*, 517 U.S. 370 (1996). The focus of the Court's inquiry in claim construction is on the objective test of what one of ordinary skill in the art would have understood the terms used in the patent claims to mean, as of the date the patent application was filed.[4] *Id* at 985-86.

In determining the proper construction of a claim, the Court has numerous sources that it may properly utilize for guidance. *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). These sources include both "intrinsic" evidence (*e.g.*, the patent specification) and "extrinsic" evidence (*e.g.*, expert testimony and the inventor's/patent owner's own descriptions of the invention). *Id.*

The starting point for any claim construction is the patent claim itself. *Pitney Bowes, Inc. v. Hewlett Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999). However, "claims are always construed in light of the specification, of which they are a part." *Netword,* 242 F.3d at 1352. "The claims are directed to the invention that is described in the specification; they do not have meaning removed from the context in which they arose." *Id.* at 1352; *Slimfold Mfg. Co. v. Kinkead Indus., Inc*, 810 F.2d 1113, 1116 (Fed. Cir. 1987) (claims are not interpreted "in a vacuum," but are read and understood in light of the specification of which they are a part).

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[4] Gen-Probe submits that, for the purposes of this motion at least, any disagreement or dispute as to the actual level and sophistication of the "person or ordinary skill" in 1987 is insubstantial at best. As of 1987, all of the inventors held doctorate degrees in molecular biology or equivalent technical disciplines. For the purpose of this motion, Gen-Probe will submit to that level of skill as "ordinary" for the Court's purposes.

Thus, when a word or phrase in a claim is used in the specification, the relevant passages must be considered in order to determine what the term means in the claim. *Renishaw PLC v. Marposs Societa' Per Azioni*, 158 F.3d 1243, 1248 (Fed. Cir. 1998). It is *always* necessary to review the patent specification as part of the claim construction process. *United States v. Adams*, 383 U.S. 39, 49 (1966) (claims are to be construed in light of the specifications and both are to be read with a view to ascertaining the invention); *Vitronics Corp.*, 90 F.3d at 1582; *Markman*, 52 F.3d at 979-80.

Ideally, the meaning of a term to one of ordinary skill in the art can be determined from the face of the patent, *e.g.*, the intrinsic evidence. *Markman*, 52 F.3d at 979-80. While the Court's primary focus is on the patent specification, reliable extrinsic evidence may also be considered:

> [I]t is entirely appropriate, perhaps even preferable, for a court to consult trustworthy extrinsic evidence to ensure that the claim construction it is tending to form from the patent file is not inconsistent with clearly expressed, plainly apposite, and widely held understandings in the pertinent technical field.

Pitney Bowes, Inc. v. Hewlett-Packard Co., 182 F.3d 1298, 1309, (Fed. Cir. 1999). In *Pitney Bowes*, Judge Michel further pointed out:

> While a judge is well-equipped to interpret the legal aspects of the document, he or she must also interpret the technical aspects of the document, and indeed its overall meaning, *from the vantage point of one skilled in the art.* ... Although the patent file may often be sufficient to permit the judge to interpret the technical aspects of the patent properly, *consultation of extrinsic evidence is particularly appropriate to ensure that his or her understanding of the technical aspects of the patent is not entirely at variance with the understanding of one skilled in the art.*

Id., *citing Mantech Envtl. Corp. v. Hudson Envtl. Servs., Inc.*, 152 F.3d 1368, 1373 (Fed. Civ. 1998) (emphasis added). These principles guide the construction of the claims of the '338 patent[5].

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[5] Gen-Probe's motion for summary judgment is based solely on the claim construction arguments expressly set forth in this memorandum. Gen-Probe believes that the claims of the '338 patent must also be limited to non-specific amplification on the basis of 35 U.S.C. § 112, paragraph six (means-plus-function, step-plus-function). Gen-Probe reserves its arguments with respect to claim construction pursuant to 35 U.S.C. § 112, paragraph six. Furthermore, Gen-Probe believes that the parties dispute still other terms of the '338 patent that are not germane to the Court's resolution of this motion.

A. The Claims of the '338 Patent

The '338 patent, Exhibit 8, consists of the specification, including drawings, and the claims. The '338 patent contains six independent claims (claims 1, 7, 19, 27, 28 and 34). Each of these claims is generally directed to a method of, or a kit for, amplifying and/or detecting a target polynucleotide (i.e., a nucleic acid), wherein the target is first isolated on a support.

Each of the claims contains a step of "amplifying" the target polynucleotide or sample. For example, claim 1 provides:

> 1. A method for amplifying a target polynucleotide contained in a sample comprising the steps of:
>
> (a) contacting the sample with a first support which binds to the target polynucleotide;
>
> (b) substantially separating the support and bound target polynucleotide from the sample; and
>
> (c) *amplifying* the target polynucleotide.

(Exhibit 8 at col. 32, ll. 27 to 33, emphasis added.) This motion concerns the proper construction of the term "amplifying" as used in the claims of the '338 patent.

B. The Teaching of the Patent

The issue of what a skilled scientist would have understood the term "amplifying" to mean is determined primarily from the specification of the patent. *Netword,* 242 F.3d at 2; *Markman*, 52 F.3d at 979-80.

In the "Background of the Invention" section, the patent defines the term "amplify" in very broad terms that encompass many different methods of amplification, including many that were already well known in the prior art. Throughout the remainder of the specification, however, the inventors teach only *non-specific* amplification because a suggested benefit of the invention is that it *eliminates* the need to design and prepare specific primers and/or the need to use specific enzymes.

Significantly, the specification sets forth four examples (Examples 4 through 7) of the amplification methods taught by the inventors. Immediately before the first example that includes an amplification step (Example 4), the inventors expressly set forth their teachings with respect to

amplification methods. Referring to the target capture methods described in Examples 1 through 3, the inventors stated:

> The sensitivity of the above DNA or RNA target capture methods can be enhanced by amplifying the captured nucleic acids. This can be achieved by ***nonspecific*** *replication using standard enzymes* (polymerases and/or transcriptases).

('338 patent, Exh. 8, at col. 30, ll. 14-18, emphasis added.)

The inventors then made clear that the reference to non-specific amplification methods was intentional and pointed out that one of the express benefits of their invention was that it permitted the use of non-specific enzymes and non-specific primers:

> Amplification of the target nucleic acid sequences, because it follows purification of the target sequences, can employ **non-specific** enzymes or primers. **Thus no specifically tailored primers are needed for each test, and the same standard reagents can be used, regardless of targets.**

(*Id.* at col. 30, ll. 30-40, emphasis added.) This teaching clearly expresses that a primary benefit of the invention is the ability to use non-specific enzymes or primers, thereby avoiding the need to craft specific primers for each particular target organism and the need to use other individualized reagents such as specific transcriptases.

C. The Examples of the Patent

Immediately following the fundamental teaching of the '338 patent as set forth above, the specification sets forth four examples of the amplification methods contemplated by the inventors ('338 Patent, Exh. 8, col. 30, l. 43 to col. 32, l. 25, examples 4-7). Consistent with the teaching of the patent that sequence-specific primers and specific enzymes are not necessary, each example suggests and describes amplification methods that use only non-specific primers and enzymes.

Example 4 illustrates "the use of RNA polymerase to amplify target DNA." ('338 Patent, Exh. 8, at col. 30, ll. 44-45.) It describes a method for amplifying the capture DNA by non-specific amplification using polymerases that lack transcriptional specificity. (*Id.* at col. 30, l. 59 - col. 31, l.17). Example 4 discloses only non-specific amplification:

> Q. So recapping the examples, examples one through three disclose capture methods without amplification?

A. Yes.

Q. And example four discloses linear *nonspecific* amplification?

A. Yes.

(Lawrie Depo., Exh. 9, at 231:7-13, emphasis added.)

Example 5 also describes a non-specific amplification method in which that the target DNA is replicated using random (*i.e.*, non-specific) primers and non-specific transcription of that DNA into RNA:

> In this example, both non-specific replication of target DNA and transcription of that DNA are used to amplify capture target DNA.... Because the primers are *random*, some will, simple (sic) as a matter of statistics, bind to and cause replication of sample sequences, no matter what those sequences are. . . .

('338 Patent, Exh. 8, at col. 31, ll. 24-54, emphasis added.) Example 5 discloses only non-specific amplification. (Lawrie Depo., Exh. 9, at 231:14-16; Richards Depo., Exh. 10., at 139:23 – 140:3.)

Example 6 describes replication of target DNA using DNA polymerase and *random* hexamer[6] oligonucleotides "to bring about *non-specific* double-stranded DNA synthesis" ('338 Patent, Exh. 8, at col. 31, ll. 63-64), using a series of repeated heat denaturation and enzyme replacement steps (*id.*, col. 31, l. 64 to col. 32, l. 19). Example 6 also discloses only *nonspecific* amplification. (Lawrie Depo., Exh. 9, at 231:17-19; Richards Depo., Exh. 10, at 140:9-13.)

Finally, Example 7 describes *non-specific* amplification using an RNA polymerase, Qß replicase:

> In this example, rRNA and RNA transcribed from target DNA is purified using a capture probe, described above. The hybrid duplex is then denatured and single stranded nucleic acids are then replicated *non-specifically* using Qß replicase...

('338 Patent, Exh. 8, at col. 32, l. 10-19.) Example 7 discloses only nonspecific amplification. (Lawrie Depo., Exh. 9, at 231:20–22; Richards Depo., Exh. 10, at 141: 3-7.)

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[6] Certain of the examples and drawings refer to "hexamer" primers. Hexamer primers are generally understood to mean random (*e.g.*, non-specific primers) used in non-specific amplification methods. (Richards Depo., Exh. 10, at 77:19 - 78:3; 133:2-9; 133:19-22.)

D. The Drawings of the Patent

The first pages of the '338 patent provide drawings of various methods encompassed by the invention. Any drawings included in the patent are a proper reference for determining claim meaning. *Wright Medical Technology, Inc. v. Osteonics Corp.*, 122 F.3d 1440, 1443 (Fed.Cir.1997) ("The proper construction of the claims is based upon the claim language, the written description portion of the specification including any relevant drawings. . . ."); *Raleigh v. Tandy Corp.*, 1997 WL 26299, *3 (N.D. Calif. Jan. 10, 1997) (interpreting "supporting means" as requiring a flat structure; "the supporting platform ... is pictured flat in the figures depicting all embodiments of the invention").

The first 3 drawings (Figure 1a to Figure 3) depict target capture methods alone, without amplification. Figures 4, 5 and 6 depict target capture followed by amplification using only non-specific primers or enzymes. The drawings included in the patent are discussed and described in the text of the patent specification ('338 Patent, Exh. 8, at cols. 10 - 19.) The text of the specification expressly states that in each of the drawings that include amplification (*id.*, Figures 4, 5 and 6) "the isolated target is *non-specifically* amplified to form a multitude of amplification products." (*Id.* at col. 15, ll. 56-58, emphasis added.)

E. As Used in the Claims of the '338 Patent, "Amplifying" Means Amplification with Non-Specific Primers or Enzymes

Reading the teaching, examples, and drawings included in the '338 patent specification, one of ordinary skill in the art could only conclude that the term "amplifying" as used in the claims means amplification methods using non-specific primers or enzymes as disclosed and taught in the patent. The patent expressly teaches that sequence-specific primers are not necessary. Therefore, a person of ordinary skill in the art would not understand the term "amplifying" as used in the claims to encompass amplification using specific primers. Similarly, based on the explicit teaching that standard, non-specific enzymes are not necessary, the ordinarily skilled practitioner of the art would not understand the term "amplifying" to encompass amplification using specific transcriptases and promoter sequences. The invention of the '338 patent cannot encompass methods that the specification states become unnecessary due to the

benefits of a target capture step prior to amplification. *See Evans Medical Ltd. v. American Cyanamid Co.*, 11 F. Supp. 2d 338, 355-56 (S.D.N.Y. 1998), *aff'd without op.*, 215 F.3d 1347 (Fed. Cir. 1999) ("There would be no quid pro quo for granting a patentee the right to exclude others from using something that his specification clearly instructs them *not* to use.").

Numerous Federal Circuit decisions demonstrate that the claims of the '338 Patent must be limited to amplification methods using non-specific primers or enzymes. Although the specification of a patent need not present every embodiment of the invention and the claims are not limited to the preferred embodiment of the invention, neither do the claims enlarge what is patented beyond what the inventor has described as the invention.

For example, in *Wang Laboratories, Inc. v. America Online, Inc.*, 197 F.3d 1377 (Fed. Cir. 1999), the patent specification described and taught only one embodiment of an invention, and the Federal Circuit held that the claims of the patent were correctly limited to that one embodiment. *Id.* at 1383. *Wang Labs* involved patent claims directed to an online information system. The accused infringer filed a motion for summary judgment of non-infringement. The outcome of the motion depended upon construction of the term "frame" as used in the patent claims. The parties agreed that the term "frame" could, in general usage, be applied to both "bit-mapped" and "character-based" displays and the specification referred generally to both types of frames. However, the examples in the patent specification described and taught character-based displays only. The district court therefore construed the term "frame" to be limited to the type of frame disclosed and described in the specification in such a manner as to constitute the invention of the patent. On appeal, the Federal Circuit affirmed.

In reaching its conclusion that the term "frame" was properly construed to be limited to the character-based displays expressly described in the specification, the Federal Circuit first found that the only systems actually described and enabled in the specification were character-based displays:

> The only system that is described and enabled in the '669 specification and drawings uses a character-based protocol. The specification mentions non-character-based protocols, for example, *in the "Background of the Invention" statement* . . . The district court viewed the references to bit-mapped protocols *as*

> *acknowledgments of the state of the art, and not as an enlargement of the invention described in the patent.* We agree, and conclude that the references to other known protocols do not describe them as included in the applicant's invention, and that the specification would not be so understood by a person skilled in the field of that invention.

Id. at 1382 (emphasis added).

The Federal Circuit then held that claims could not be interpreted to have a meaning or scope that would lead to their invalidity:

> Wang argues that it is irrelevant to the construction of the claims whether the specification contains an enabling description of any bit-mapped decoder, stating that enablement is a requirement for validity, not a factor in claim construction. However, the claims are not properly construed to have a meaning or scope that would lead to their invalidity for failure to satisfy the requirements of patentability.

Id. at 1382-83. The court next held that the requirements of 35 U.S.C. § 112 (written description and enablement[7]) would not be met with respect to protocols other than character-based frames:

> Although Wang is correct that a claim is not invalid simply because it embraces subject matter that is not specifically illustrated, in order to be covered by the claims that subject matter must be sufficiently described as the applicant's invention to meet the requirements of section 112. This requirement was not met as to protocols other than character-based.

Id. at 1383.

The Federal Circuit then rejected the patentee's argument that character-based protocols were simply a preferred embodiment:

> Wang states that the character-based protocol is simply a preferred embodiment and that the embodiment described in the specification does not set the boundaries of the claims citing *Comark Communications, Inc. v. Harris Corp.*, 156 F.3d 1182, 1186, 48 USPQ2d 1117, 1124 (Fed. Cir. 1998), for its statement that limitations from the specification are not to be read into the claims. AOL and Netscape respond that when the subject matter that is claimed is the only subject matter that is described and enabled in the specification, that is the invention itself, and not simply a "preferred" example of a broader invention that is not described and enabled.... Whether an invention is fairly claimed more broadly than the "preferred embodiment" in the specification is a question

[7] 35 U.S.C. § 112 provides in pertinent part: "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention."

> specific to the content of the specification, the context in which the embodiment is described, the prosecution history, and if appropriate the prior art, for claims should be construed, when feasible, to sustain their validity. The usage "preferred" does not of itself broaden the claims beyond their support in the specification.... *The only embodiment described in the '669 patent specification is the character-based protocol, and the claims were correctly interpreted as limited thereto.*

Id. at 1382 (empahsis added), *citing Modine Manufacturing Co. v. United States International Trade Commission*, 75 F.3d 1545, 1551 (Fed. Cir. 1996), the court explained that "when the 'preferred embodiment' is described as the invention itself, the claims are not entitled to a broader scope than that embodiment." 197 F.3d at 1383.

Wang Labs is directly analogous to the facts in this case. Both cases involve a summary judgment motion of non-infringement. Both cases involve a claim term that could be construed narrowly based on the patent specification or more broadly based on general usage. In *Wang Labs*, the claim term "frame" had a meaning in general usage that encompassed both bit-mapped and character-based protocols and the "Background of the Invention" section contained references to support that meaning. In this case, too, the term "amplifying" has a meaning in general usage that might encompass both specific and non-specific amplification.

Both *Wang Labs* and the instant case involve specifications that describe and teach only one aspect or embodiment of the claim term at issue. In *Wang Labs*, the specification described and taught only character-based display frames. While there were references in the specification to other types of frames, the court found that these were not described in such a way as to be included in the applicant's invention. Similarly, in the instant case, the specification describes and teaches only non-specific amplification. Indeed, the specification states that the ability to use non-specific primers and enzymes is a primary benefit of the '338 invention. Here, too, as in *Wang Labs*, the patent obviously does not "enable" an invention that it does not describe, and the claims should not be construed in such as manner as to render them invalid for lack of enablement. Thus, the holding in *Wang Labs* is particularly applicable to this motion for summary judgment, and the term "amplifying" as used in the claims of the '338 patent must be limited to non-specific amplification with the primers or enzymes described in the '338 specification. Any other result

would mean that the claims cover methods of amplification using specific primers or enzymes that are not described nor taught in the '338 Patent and which the patent says can be avoided.

In *SciMed Life Systems, Inc. v. Advanced Cardiovascular Systems, Inc.*, 242 F.3d 1337 (Fed. Cir. 2001), the Federal Circuit also held that a claim term was to be construed to be limited in accordance with the specific embodiments disclosed in the specification. The Federal Circuit held in *SciMed Life* that the term "lumens" in certain patent claims, although not limited by the claims themselves, was required to be construed to encompass only *coaxial* lumens, and not to encompass "dual" or "adjacent" lumen configurations. The court based its ruling on the fact that all embodiments in the patent specification were limited to coaxial lumens, and that the specification highlighted that one of the advantages of the invention was the use of the coaxial lumens. *Id.* at 1342-43. Likewise, in the instant case, all of the examples in the '338 patent specification involving amplification are limited to non-specific amplification, and the specification highlights the advantage obtained because the need for specific primers and enzymes may be avoided. Therefore, just as in *SciMed*, the '338 Patent's claims must be limited to non-specific amplification.

This conclusion is also supported by *O.I. Corp. v. Tekmar Co.*, 115 F.3d 1576 (Fed. Cir. 1997). *O.I. Corp.* involved the meaning of the word "passage" in a claim. The court held that the term "passage" was limited to non-smooth or conical types of passages because the only passage structures contemplated by the specification were non-smooth or conical:

> All of the "passage" structures contemplated by the written description are thus either non-smooth or conical. In addition, the description expressly distinguishes over prior art passages by stating that those passages are generally smooth-walled. OI has not identified anything in the prosecution history contrary to those statements. Therefore, we conclude that one skilled in the art reading the claims, description, and prosecution history would conclude that the term "passage" in claim 17 does not encompass a smooth-walled, completely cylindrical structure.

Id. at 1581.

The facts of *O.I.* are analogous to the instant case. In *O.I.*, while the claim contained the general term "passages," the specification described only non-smooth or conical passages. Likewise, while the '338 Patent claims contain the general term "amplifying," the specification

describes only non-specific amplification methods and states that specially tailored primers and specific enzymes are not necessary when the invention is used.

The case of *Kraft Foods, Inc. v. International Trading Co.*, 203 F.3d 1362 (Fed. Cir. 2000) is also directly applicable to the instant case. The Federal Circuit found that the term "protecting back panel" was properly construed as limited to a "relatively stiff" panel because that was the only type of back panel described in the specification. 203 F.3d at 1367-69. The court reached this conclusion despite the fact that other claims did not expressly contained a "relatively stiff" limitation:

> Notwithstanding Kraft's contentions, we agree with the district court that the written description and prosecution history overcome any presumption arising from the doctrine of claim differentiation, and thus approve the district court's construction of claim 2's protecting back panel as one that must be relatively stiff. . . . With respect to the written description, every disclosed embodiment that employs a back panel employs one that is relatively stiff. . . .

Id. at 1368. Thus, *Kraft* provides additional support for the conclusion that the term "amplifying" in the '338 Patent claims must be construed as meaning non-specific amplification.

Other decisions have similarly determined that claims terms must be determined to be consistent in scope with the disclosures of the specification. *See, e.g., Netword,* 242 F.3d at 1353 (district court correctly construed "local server computer" to mean a local server computer that has a limited database of aliases and that may request updates from a central registry computer); *Toro Co. v. White Consolidated Industries, Inc.*, 199 F.3d 1295, 1301-02 (Fed. Cir. 1999) ("cover" interpreted to encompass only permanently attached covers because specification disclosed only attached covers and described advantages of unitary structure as important to the invention); *Biogen, Inc. v. Berlex Labs, Inc.*, 113 F. Supp. 2d 77, 98 (D.Mass. 2000) ("cell incorporating a DNA construct" limited to a cell containing the particular DNA construct specifically described in the specification).

The analysis in these cases is directly applicable to the claim construction issue presented here. At numerous points, the '338 specification describes the claimed invention only in terms of using non-specific primers or enzymes and states that this characteristic is an advantage of the invention. Read together, these portions of the specification lead to the inescapable conclusion

that "amplifying" would have been understood by one skilled in the art at the time the patent application was filed to mean non-specific amplification using non-specific primers or enzymes.

F. Extrinsic Evidence Confirms the Claim Construction

In addition to the ample intrinsic evidence presented in the specification to show that the investors intended to limit their invention to non-specific amplification techniques and that intention is apparent to one of ordinary skill, ample extrinsic evidence exists to confirm that intention and interpretation. One of the sources of information that the Court may properly consider in claim construction is the declaration of an expert witness. Rule 702, Fed. R. Evid.; *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 589 (1993); *Pitney Bowes*, 182 F.3d at 1308-09 (Fed. Cir. 1999) (consultation of extrinsic evidence appropriate to ensure that claim construction is not entirely at variance with the understanding of one skilled in the art). Gen-Probe has submitted the declaration of Joseph O. Falkinham III, Ph.D., which confirms what is apparent from the face of the patent: One of ordinary skill in the art would have understood the term "amplifying" in the '338 patent to include only the non-specific amplification methods taught by the patent. One of ordinary skill in the art would not have understood the term "amplifying" to include other amplification methods that use sequence-specific primers or enzymes.

Testimony from one of the inventors and from other witnesses confirms this conclusion. In 1983 Dr. Kary Mullis invented a form of specific amplification using sequence-specific primers, called the "polymerase chain reaction." Dr. Mullis received the Nobel Prize in chemistry for his invention. If the inventors had intended to suggest and claim the combination of target capture with specific primer methods of amplification such as PCR, it would have been easy for them to do so.

The PCR method was first described at a scientific meeting in the summer of 1985 and was published in December 20, 1985. Saiki et al., "Enzymatic amplification of beta-globin genomic sequences and restriction site analysis for diagnosis of sickle cell anemia," SCIENCE 230:1350-54 (1985). Within the scientific community, PCR was immediately "big news." (Richards Depo, Exh. 10, at 38:6-8.) Although the application leading to the '338 patent was filed two years after the disclosure of PCR, the patent does not disclose or teach the combination of target capture with

amplification methods using specific primers, such as PCR.

While the '338 inventors could have included an example that showed the combination of target capture and sequence-specific amplification (such as PCR), they instead described in the specification a method that permitted scientists to *avoid* the use of sequence-specific primers. That is, the inventors chose to describe their invention as an *alternative* to specific primer methods such as PCR. This conclusion, which is inescapable from reading the specification, is supported by testimony from the inventors concerning the nature of their invention. Inventor Jon Lawrie testified that the patent was meant to cover *new* amplification methods using non-specific primers, not already-known methods such as PCR:

> Q. Can you recall any reason that a reference to PCR might have been intentionally omitted from the patent application?
>
> A. Yes....
>
> Q. If there's no reference in the ['338] patent to combining target capture with PCR, do you have any explanation as to why it is not there?
>
> A. I believe that it was a separate, the thought behind this [referring to the '338 patent] was coming up with *new* methods of amplification, not old ones.
>
> Q. For the purposes of what you just said you classify PCR as an old method of amplification?
>
> A. PCR itself was described in the patent, issued patent [e.g., it was an "old" method].
>
> Q. And your understanding of the 338 patent was that it was directed to other methods of amplification?
>
> A. The, it was, it was directed to the methods disclosed by, you know, *the methods separate from PCR*.
>
> Q. Those being the methods, for example, as the methods set forth in example six and seven?
>
> A. Yes.

(Lawrie Depo., Exh. 9, at 178:19 - 180:11.)

> Q. However, your recollection of why - of if there's no - your explanation of why there might not be a reference to PCR in the patent is that the patent wasn't intended to cover old methods of amplification such as PCR; is that right?

A. The patent was intended to cover the discoveries by myself, Halbert and King that there should be in some, you know, disclosure back at Amoco. That's what the patent was about. Why PCR was left out I can just speculate. It wasn't what we came [up] with, it was in the previous, it was a previous older method.

Q. You were looking for other things?

A. Yeah.

(*Id.* at 180:23 – 181:13.)

Dr. Lawrie's testimony explains why the inventors of the '338 patent described and taught only amplification with non-specific primers or enzymes. They considered that particular combination to *be* their invention. They believed that once "specificity" was added to the overall process by the use of capture probes, it was not necessary to use specific primers or enzymes in the amplification step. The combination of specific target capture and *non-specific* amplification was what the inventors believed they had invented, that is what the '338 patent teaches, and that is all the claims of the '338 patent -- properly construed -- encompass.

Although the Federal Circuit has routinely cautioned District Courts not to rely upon self-serving inventor testimony to *expand* the scope and construction of patent claims, the Court and other District Courts have recognized the significant evidentiary and persuasive value of extrinsic evidence provided by admissions by inventors and patent owners that confirm the limited scope of patent claims. For example, in *Jonsson v. Stanley Works*, 903 F.2d 812 (Fed. Cir. 1990), the Federal Circuit affirmed a district court's order narrowly construing patent claims consistent with the admissions against interest of the inventor. *Id.* at 818. Dr. Lawrie's testimony satisfies the well-settled view of relevance in this instance. *See Components, Inc. v. Western Electric, Co.*, 52 F.R.D. 379, 382 (D. Me. 1971); *Canadian Ingersoll-Rand Co., Ltd. v. Peterson Products of San Mateo, Inc.*, 350 F.2d 18, 24 (9th Cir. 1965).

Other evidence reinforces Dr. Lawrie's testimony. On December 15, 1989, Dr. James C. Richards, the Director of Business Development and Licensing for Gene-Trak Systems, admitted that the '338 patent encompassed only amplification with non-specific primers and explicitly contrasted the methods of the patent with other methods of amplification using specific primers.

Dr. Richards' analysis was set forth in a letter to one of Gene-Trak's partners, Amoco Technology Company. (See Exhibit 1)

Dr. Richards first discussed the fact that the pending patent application encompassed the use of random, non-specific primers. He then discussed the effect of combining non-specific amplification with the use of an initial target capture step. Finally, he pointedly contrasted the invented method with other known methods that used specific primers or promoters (*e.g.*, enzymes):

> Cetus, Sibia/Salk, Biotechnica, etc. all claim **specific** primers for amplification whereas the present invention claims uses of the opposite, namely, **non-specific** primer or promoters.... Following extensive washing, captured target polynucleotides could be released and the non-specific amplification process could take place.

(Exhibit 1 at page 2, emphasis in original).

At the time he wrote this letter, Dr. Richards held a Ph.D. in Microbiology and Biochemistry from Southern Illinois University. (Richards Depo., Exh. 10, at 7:17-20.) He had worked at Amoco from February 1984 to October 1986, when he moved to Gene-Trak. (*Id.* at 28:1 - 29:2-4.) At Amoco, Dr. Richards worked with the four inventors of the '338 patent, and Dr. Lawrie had explained to him the nature of the invention that is the subject of the patent. (*Id.* at 30:5-11; 35:13 – 36:16.)

From October 1986 to December 1989 when he wrote the letter, Dr. Richards worked at Gene-Trak[8] with the four inventors. (*Id.* at 29:2-4; 41:10-12.) As Gene-Trak's Director of Business Development and Licensing, Dr. Richards managed the company's technology assets and technology needs. (*Id.* at 44:18 – 45:9.) As part of his job, Dr. Richards evaluated numerous technologies and participated in licensing negotiations. (*Id.* at 47:22 – 48:24.)

When presentations on patent matters, including target capture patents, were made to the Gene-Trak partnership committee and to the Gene-Trak scientific advisory board, Dr. Richards made those presentations. (*Id.* at 60:8-13; 82:3-6; 150:9-14; 151:1-4.) Dr. Richards was a member of the Gene-Trak patent committee and discussed patents with Gene-Trak's patent counsel. (*Id.* at

[8] Gene-Trak was a partnership formed by Amoco and Integrated Genetics in the summer of 1986. Gene-Trak Systems became Vysis in 1991.

150:15-21.)

When Dr. Richards wrote his December 1989 letter, his sources of knowledge about the application for the '338 patent were discussions he had held about the patent application with Tony Janiuk, Gene-Trak's patent counsel, and with inventor Dr. Jon Lawrie. (*Id.* at 152:5-13; 186:11-21.) In his December 1989 letter to senior management, Dr. Richards tried to be as accurate as possible, and he has never since concluded that the way he described the invention was inaccurate. (*Id.* at 154:9 - 156:12; 164:17-22; 165:14-19.) Dr. Richards' letter makes clear that the invention of the '338 patent was the use of target capture *with non-specific amplification*, in express contrast to methods that use specific primers or enzymes.

G. Conclusion: The Claims Cover Only Target Capture Combined With Non-Specific Amplification

The interpretation to be given a term in a patent claim can only be determined and confirmed with a full understanding of what the inventors actually invented and intended to include within the claim. *Wang Labs,* 197 F.3d at 1384; *Renishaw,* 158 F.3d at 1250. An inventor is entitled to claim only the invention described in the specification. Claims in a patent may not be validly construed to be broader than the supporting disclosures of the specification. *Gentry Gallery, Inc. v. Berkline Corp.,* 134 F.3d 1473, 1479-80 (Fed. Cir.1998).

The written description of the invention set forth in the patent specification is used to determine what a person skilled in the art would conclude the inventor had actually invented. *Markman,* 52 F.3d at 979. The claim construction that most naturally aligns with the patent's description of the invention will be, in the end, the correct construction. *Renishaw,* 158 F.3d at 1250.

In this case, the patent specification describes the invention of a method that combines target capture with non-specific amplification. The patent specifically teaches, as a primary benefit of the invention, that "specially tailored primers are not necessary" and that the "same standard amplification reagents can be used, regardless of the targets." Each of the examples and each of the drawings describes only amplification methods that use non-specific primers or enzymes. The inventors clearly taught that by adding specificity to a nucleic acid assay in the

target capture step, they had enabled scientists to avoid the use of specific primers and enzymes in the amplification step of the assay.

Under these circumstances, one of ordinary skill in the art as of December 1987 would have understood from the specification that the inventors' method combined target capture and non-specific amplification. This conclusion is reinforced by Dr. Lawrie's testimony that the invention was intended to provide new alternatives to sequence-specific amplification methods, such as PCR. This conclusion is made unavoidable by Dr. Richards' December 1989 description of the invention, in which he expressly contrasted the invention with other methods that use specific primers or promoters.

IV. GEN-PROBE IS ENTITLED TO SUMMARY JUDGMENT THAT ITS TMA PRODUCTS DO NOT LITERALLY INFRINGE THE CLAIMS OF THE '338 PATENT

After the claims have been construed, the next step in an infringement analysis is the comparison of the claims to the product at issue. *Carroll Touch, Inc. v. Electro Mechanical Sys., Inc.*, 15 F.3d 1573, 1576 (Fed.Cir. 1993). Here, Gen-Probe moves for summary judgment only on the issue of literal infringement. Literal infringement of a claim requires that the accused device contain each and every limitation of the claim. *Bayer AG v. Elan Pharm. Research Corp.*, 212 F.3d 1241, 1247 (Fed. Cir. 2000). If even one claim limitation is absent from the product at issue, there can be no literal infringement as a matter of law. *See Mas-Hamilton Group v. LaGard, Inc.*, 156 F.3d 1206, 1211 (Fed. Cir. 1998).[9]

In this case, Gen-Probe's HIV-1/HCV Assay use a target-specific amplification technology called Transcription-Mediated Amplification (TMA). (Longiaru Declaration, ¶5.) TMA uses *specific* primers, *specific* promoters, and a *specific* polymerase enzyme that recognizes only those promoters. Gen-Probe's product does not use non-specific amplification. (*Id.* at ¶¶ 6-11.) Thus, the Gen-Probe product is not covered by the '338 Patent claims, which encompass only

[9] Notwithstanding the absence of literal infringement and the foregoing evidence that the inventors did not intend to claim and certainly did not invent specific amplification techniques, Vysis may yet contend that Gen-Probe's TMA products infringe the claims of the '338 patent under the doctrine of equivalents. As noted here, however, Gen-Probe has expressly limited the scope of this motion and the Court's order to the issue of literal infringement. If necessary, Gen-Probe will address the issue of the doctrine of equivalents separately.

non-specific amplification. Accordingly, as a matter of law Gen-Probe's use, manufacture and sale of this product are not within any of the claims of the '338 Patent. *See Mas-Hamilton*, 156 F.3d at 1211.

V. CONCLUSION

For the foregoing reasons, the Court should enter partial summary judgment on Counts One and Three confirming that Gen-Probe's HIV-1/HCV Assays do not literally infringe the claims of the '338 patent.

April 30, 2001

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